Inflammation 2007 - Eighth World Congress (Part II) - OVERNIGHT REPORT

16-20 June 2005, Copenhagen, Denmark

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Mast cells and eosinophils in allergy

The first talk of the day was the honorary lecture given by Francesca Levi-Schaffer (Hebrew University), who was awarded the IAIS Woman in Sciences Award. Following a lively acceptance speech, the presentation focused on the cellular players in allergic inflammation. Historically, mast cells have been viewed as the most important initiators of the allergic response, giving way to eosinophils, which maintain the response through late-phase inflammation. Professor Levi-Schaffer suggested, however, that the allergic response is not as compartmentalized as this, and that it is more of a continuum comprising mast cell and eosinophil interactions. The two cell types interact via soluble mediators, such as tryptase, which stimulates cytokine production by eosinophils, and major basic protein, which induces mast cell histamine release, and also via cell-cell interactions such as TRAIL-ligand 7/TRAIL and Nectin-2/DNAM-1.

The talk then turned to the interaction between these cell types as a potential immunopharmacological target for therapeutic intervention in allergy. Downregulation of the system could be achieved, for example, by inhibiting an activatory receptor or activating an inhibitory receptor. Eosinophils are activated by CD48, and expression of this antigen is increased on eosinophils from atopic asthmatics. Professor Levi-Schaffer described how neutralization of CD48 abrogates lung inflammation and mucus production in ovalbumin-challenged rodents. The inhibitory receptor IRp60 (CD300a) is expressed on various cells, including T-cells, natural killer cells and neutrophils. Although its ligand is still unknown, it has been shown to inhibit both mast cells and eosinophils, inhibiting eosinophil chemotaxis and IL-5-mediated JAK2, ERK1/1 and p38 phosphorylation. Professor Levi-Schaffer's laboratory has created bispecific antibody fragments that bind IgE and IRp60, or CCR3 and IRp60. The latter fragment has been found to reverse chronic asthma in mice when dosed from day 28 once inflammation is already established.

ARRY-797 proves safe and effective in a phase I trial

Kevin Koch of Array Biopharma presented new phase I data on ARRY-797, a member of a novel structural class of p38 MAP kinase inhibitors designed to have high selectivity against a panel of more than 200 kinases, and in a receptor and ion channel screen. Indicated for cancer and inflammation, ARRY-797 is currently undergoing a single-ascending-dose phase I study. Healthy volunteers received 25, 50, 100, 200, 300 or 400 mg of oral ARRY-797, which resulted in dose-dependent drug exposure that was well tolerated, with no serious adverse events or changes in blood chemistries observed. Peak drug plasma concentration was found to be approximately 20 ng/ml at the 50-mg dose, and the half-life was 2.5 h. Blood samples taken at multiple timepoints were stimulated ex vivo with LPS and analyzed for cytokine expression. IL-1 beta, TNF-alpha and PGE2 were inhibited both time- and concentration-dependently. At the 50-mg dose, greater than 80% inhibition was observed, and found to last for more than 4 h. At the higher dose, extensive cytokine knockdown occurred. PGE2 was measured as a surrogate in order to assess the potential of the drug as an analgesic.

Dr Koch noted that a multiple-ascending-dose trial of ARRY-797 in healthy volunteers was initiated in June 2007, and clinical trials of the drug for inflammatory diseases are planned. An IND for phase I studies in advanced hematological cancers was filed in April 2007, with an anticipated start date of later in the year. Phase II studies are expected to start in early 2008.

In preclinical studies, ARRY-797 augmented the activity of cisplatin and temozolomide. Although it did not display significant activity as a monotherapy in most of the models tested, as a single agent in the multiple myeloma RPMI 8226 xenograft model, it inhibited tumor growth by 72%.

In April 2007, a CE Unterberg Towbin analyst noted that a "clean safety signal (no liver or CNS toxicities)" from the phase I trial would be a significant positive due to toxicity issues seen with previous p38 inhibitors. This analyst believed that ARRY-797 had been designed to avoid these side effects by having reduced blood-brain barrier penetration and high selectivity.

New preclinical data

Christopher S Stevenson from Novartis presented data on the company's broad-spectrum matrix metalloprotease (MMP) inhibitor, PKF-242-484, in an MMP-12-inducing smoke exposure model. The effect of the drug when given 1 h before and 5 h after exposure was tested in BALB/c and C57/BL6 mice. A 10-mg/kg dose reduced lung neutrophilia in BALB/c mice by 45 and 60% when administered orally and intranasally, respectively. No effect was seen in the C57/BL6 mice. With oral and intranasal dosing in both mouse strains, there was a trend towards increased or decreased macrophage infiltration, respectively. PFK-242-484 did not affect smoke-increased levels of IL-1beta, KC or MIP-2. In previous acute lung inflammation mouse models studies, PKF-242-484 was shown to reduce neutrophil and lymphocyte influx and TNF alpha release into the airways.

Data from efficacy studies of Osprey Pharmaceuticals' leukocyte population modulator OPL-CCL2-LPM in anti-thymocyte serum-induced mesangioproliferative glomerulonephritis in rats were presented by the company's Laura McIntosh. The compound is an anti-CCL2 recombinant fusion protein comprising a chemokine-binding moiety linked to the Shiga-A1subunit toxin. Rats received anti-thymocyte serum on day 0, and 50 or 100 microg/kg of OPL-CCL2-LPM intravenously every other day from day 2 to day 8. Results demonstrated that the drug reduced glomerular lesions, macrophage count, fibronectin and smooth muscle actin by 40, 36, 38 and 28%, respectively. Urine protein levels were decreased by 35 and 39% in the 50- and 100-microg/kg dose groups, respectively. In preliminary animal studies, the drug showed no systemic toxicity.

ProMetic BioSciences' PBI-1393, which entered phase Ib/II trials for cervical cancer in January 2007, is also being investigated for the potential treatment of inflammation. The company's Mustapha Allam presented data showing that in vitro the drug decreased LPS-induced TNF-alpha production by human polymorphonuclear cells by 22 and 35% at drug concentrations of 10(-7) M and 10(-9) M, respectively. In vivo, in the rat air pouch model, 25 and 100 mg/kg of PBI-1393 decreased LPS-induced TNF-alpha by 47 and 53%, respectively. The 100-mg/kg dose decreased MCP-1 and PGE2 by 16.3 and 29.2%, respectively. As leukocyte infiltration was not significantly inhibited by either of the two doses, the results suggest the involvement of a common TNF-alpha and PGE2 pathway second messenger.

Christina Furebring from Alligator Bioscience presented data on her company's ongoing development of recombinant variants of the chemotaxis inhibitory protein of Staphylococcus aureius (CHIPS). CHIPS blocks the C5a-receptor (C5aR) and inhibits neutrophil chemotaxis, but due to its bacterial origin, most individuals have antibodies that interfere with its action, hence the need to use recombination to restore its efficacy. In the study, several clones were selected that inhibited C5aR signaling, and that required approximately a 1000-fold increase in anti-CHIPS IgG in order to inhibit them. Alligator expects to have lead candidates by the end of summer 2007, and then plans to seek a partner for clinical trials.

New inflammation data on Serono Pharmaceutical Research Institute's MEK protein kinase inhibitor program were presented by Vittoria Ardissone of Merck Serono. AS-701820, which showed an IC50 value of 2 mg/kg against LPS-induced TNF-alpha production, was assessed in established collagen-induced rheumatoid arthritis in mice. Administered orally at 10, 30 and 100 mg/kg, twice daily for 7 days, the drug was shown to decrease inflammatory and erosive lesions. Clinical disease score was reduced by the 30- and 100-mg/kg regimes. Serono's MEK inhibitors are also under investigation for the potential treatment of cancer, and have to date, shown promising results in vitro and in animal models.